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Synthesis of 2H-1,2-oxaphosphorin 2-oxides

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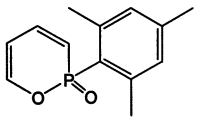
Abstract

Two novel heterocyclic dienes, 2-ethoxy-3-phenyl-2*H*-oxo-1,2-oxaphosphorin 2-oxide (**3**) and 5-bromo-2-ethoxy-3-phenyl-2*H*-oxo-1,2-oxaphosphorin 2-oxide (**4**), are described. They were prepared in four steps starting from 2-ethoxy-3-phenyl-1,2-oxaphosphorinane 2-oxide (**12a**,**b**) (*trans* and *cis*) by a bromination–dehydrobromination sequence. Free radical bromination of **12a**,**b** with NBS/AIBN furnished two isomeric bromides **13a**,**b**. Isomer **13b** gave 2-ethoxy-5,6-dihydro-3-phenyl-2*H*-1,2-oxaphosphorin 2-oxide (**14**) on treatment with LiCl/DMF. Isomer **13a** underwent C–OEt bond cleavage followed by HBr elimination to give the phosphonic acid **17**. Treatment of **14** with NBS/AIBN afforded isomeric 5-bromo-2-ethoxy-5,6-dihydro-3-phenyl-2*H*-1,2-oxaphosphorin 2-oxides (**15a**,**b**) and 5,5-dibromo-2-ethoxy-5,6-dihydro-3-phenyl-2*H*-1,2-oxaphosphorin 2-oxide (**18**), separated by chromatography. Dehydrobromination of **15a**,**b**, and **18** with an excess of Et_3N in toluene at 80–95 °C provided the target dienes **3** and **4**, respectively.

Keywords: Phosphorus heterocycles; 2*H*-1,2-Oxaphosphorin 2-oxide; Bromination; Synthesis; Dehydrobromination

1. Introduction

Analogs of α-pyrone have been of considerable interest to synthetic chemists because of their biological properties [1–7]. The activity of α-pyrones as HIV protease inhibitors sparked additional interest in the investigation of these compounds [1,2]. Sulfur and selenium intracyclic analogs of α-pyrone exhibited strong photobiological activity [8]. Furthermore, pyrones are valuable substrates in the Diels–Alder reaction as precusors for more complex systems [6,7,9–13]. By contrast, only two phosphorus analogs of α-pyrone (**1** and **2**) have been previously synthesized [14,15]; important steric or electronic effects accounted for their stability.



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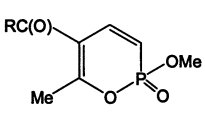

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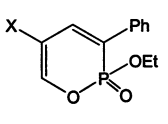

3 X = H
4 X = Br

Due to our interest in the physico-chemical properties of non-stabilized phosphorous α-pyrone analogs, we undertook synthesis of two 3-phenyl-2*H*-oxo-1,2-oxaphosphorin 2-oxides **3** and **4**. The synthetic pathway allowed isolation of several 5,6-dihydro-3-phenyl-2H-1,2-oxaphosphorin 2-oxide derivatives which may serve as valuable synthetic intermediates.

2. Results and discussion

2.1. Bromination–dehydrobromination of phostone (5)

Prior work in our laboratory on the synthesis of 2-ethoxy-1,2-dioxaphosphorinane **5** (phostone) and its derivatives [16–18] suggested the use of **5** as a starting material. Bromination–dehydrobromination of **5** was expected to provide the cyclic diene, 2-ethoxy-2H-1,2-oxaphosphorin **9** (Scheme 1).

Free radical bromination of **5** with NBS in the presence of AIBN in CCl_4 was unsuccessful. However, **5** was brominated by treatment with LDA in bromine–THF (Scheme 2) to give a 1:1 mixture of monobro-

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